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Research report

Genetic variations in the dopamine reward system influence exercise reinforcement and tolerance for exercise intensity

Kyle Flack[a,b,*], Christopher Pankey[b,c], Kelsey Ufholz[b], LuAnn Johnson[b], James N. Roemmich[b]

[a] Department of Dietetics and Human Nutrition, University of Kentucky, Lexington, KY, USA
[b] USDA, Agricultural Research Service, Grand Forks Human Nutrition Research Center, 2420 2ndAve N., Grand Forks, ND, USA
[c] Department of Biomedical Sciences, West Virginia School of Osteopathic Medicine, Lewisburg, WV, USA

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ABSTRACT

Background: : Exercise is a reinforcing behavior and finding exercise highly reinforcing is characteristic of habitual exercisers. Genotypes related to dopamine metabolism moderate the reinforcing value of behaviors, but genetic moderators of exercise reinforcement have not been established.
Purpose: : Determine whether singular nucleotide polymorphisms (SNPs) that moderate central reward pathways and pain neurotransmission are associated with exercise reinforcement, tolerance for exercise intensity, and usual physical activity.
Methods: : Adults (n = 178) were measured for the reinforcing value of exercise relative to sedentary activities ($RRV_{exercise}$), minutes of moderate-to-vigorous physical activity (MVPA) and completed the Preference for and Tolerance of the Intensity of Exercise Questionnaire. Genotyping of 23 SNPs known to influence central dopamine tone, pain, or physical activity was performed. ANOVA tested differences in $RRV_{exercise}$, tolerance, and MVPA among genotype groups. Linear regression controlling for BMI, sex, and liking of exercise was used to further predict the association of genotype on $RRV_{exercise}$, tolerance, and MVPA.
Results: : Having at least one copy of the G allele for the DRD2/ANKK1 polymorphism (rs1800497) conferred greater $RRV_{exercise}$. Greater tolerance for exercise intensity was observed among those homozygous for the T allele for the CNR1 polymorphism (rs6454672), had at least one copy of the G allele for the GABRG3 polymorphism (rs8036270), or had at least one copy of the T allele for the LPR polymorphism (rs12405556). Homozygous individuals for the T allele at rs6454672 exhibited greater MVPA.
Conclusion: : Similar to other reinforcing behaviors, there is a genetic contribution to exercise reinforcement, tolerance for exercise intensity, and MVPA.

1. Introduction

Physical activity (PA) and the exercise subcomponent of PA are well-established as effective strategies to improve the health of nearly every organ system in the body, increase energy expenditure, and promote maintenance of a healthy body weight [1]. Despite the long-term public health emphasis by the US government regarding the importance of PA for the health of Americans, more than 90% of US adults fail to meet PA recommendations when objectively assessed by accelerometry, and just 1 in 4 Americans report engaging in any leisure time physical activity [2,3]. Producing sustained increases in exercise and PA is an intractable problem; interventions designed to increase long-term PA have not yet demonstrated adherence in efficacy trials, let alone effectiveness trials [4].

Understanding individual-level factors associated with exercise participation may help to solve the problem of low adherence to the physical activity guidelines. One such factor is the reinforcing value of exercise relative to a competing alternative behavior (relative reinforcing value of exercise, $RRV_{exercise}$). The alternative behavior is often a desired sedentary activity such as screen time or reading that is often chosen in favor of physical activity/exercise. Exercise reinforcement is a measure of how much an individual is willing to work to gain access to (i.e., consume) exercise. Individuals who find a behavior highly reinforcing will perform more work to obtain access relative to a less reinforcing behavior [5]. Indeed, the $RRV_{exercise}$ is associated with engaging in physical activity at a frequency, duration, and intensity sufficient to meet physical activity guidelines [6], the choice to be physically active among children [7], and predictive of habitual vigorous PA among adults [8].

The dopamine hypothesis of reward explains that behavioral

* Corresponding author at: University of Kentucky, 206E Funkhouser Building, Lexington, KY 40506-0054, USA.
E-mail address: Kyle.Flack@uky.edu (K. Flack).

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reinforcement and the appetitive drive to consume a reward are predominately a function of the meso-accumbal dopamine system [9,10]. At the core of this system, specific genotypes explain some of the individual variability in the reinforcing nature of, and participation in behaviors such as drug abuse, alcohol consumption, nicotine use, gambling, and eating [5,11–13]. For example, SNP's influencing protein expression for the DRD2 or DRD3 dopamine receptors are associated with opioid addiction, alcoholism, cocaine abuse, and smoking [14–16]. Also, SNPs affecting central dopamine tone such as the dopamine transporter gene (SLC6A3), DRD2 receptor, monoamine oxidase A (MAOA-LPR), and serotonin receptor genes are associated with food reinforcement and energy intake [17], while SNPs of the fat mass and obesity associated (FTO) gene moderate the relationship between food reinforcement and energy intake [18].

Exercise can be realized as a reinforcing behavior as exercise dependency has been demonstrated in both humans [19,20] and rodents [21–23]. The wide individual differences in successful adherence to regular PA and exercise [2] suggest that genetic variability in central mechanisms of reinforcement may be associated with individual differences in $RRV_{exercise}$, although this has not yet been studied. Identifying such variations in the central dopaminergic reward system would provide initial evidence that some SNPs may moderate exercise reinforcement, thus influencing individual differences in physical activity behaviors [9,24] and adherence to physical activity guidelines [6]. Prior work suggests that SNPs involved in control of the central dopaminergic reward system may associate with PA behavior [25,26]. SNPs associated with pain neurotransmission could additionally impact exercise reinforcement [27,28] because exercise reinforcement is positively associated with the ability to tolerate the discomfort of increasing exercise intensity [6]. Thus, the current study was performed to test the hypothesis that SNPs associated with central dopamine physiology that moderate the reinforcing value of other behaviors [17,29,30], activity of central nervous system reward pathways [9,14,16,31,32], or those associated with pain neurotransmission [27,28] would be associated with exercise reinforcement, tolerance for exercise intensity discomfort, and usual (habitual) physical activity.

2. Materials and methods

2.1. Participants and study design

The study sample was a combined data set from two studies on exercise reinforcement. One study was a cross-sectional study to determine predictors and correlates of exercise reinforcement (clinical trials.gov identifier: NCT02416882) while the other was a longitudinal study on changes in exercise reinforcement (clinical trials.gov identifier: NCT02444247). The baseline assessment of exercise reinforcement from the longitudinal study was used for the present analysis. A total of 178 participants (127 female) age 18 to 49 years were included. Baseline participant characteristics are presented in Table 1. Participants were a sample who responded to recruitment media including printed brochures, fliers, and online advertisements placed on the Grand Forks Human Nutrition Research Center website. Entry criteria were very similar for both studies. All participants were non-smokers and healthy enough to participate in an exercise program assessed by a physical activity readiness questionnaire, not taking any drugs that affect energy expenditure (e.g., thyroid, glucose-lowering drugs), could not have gained or lost more than 5% of body weight over the past 6 months or 10 pounds over the past 3 months, could not use tobacco, and could not be pregnant or lactating or plan to become pregnant in the next 6 months. Both studies were approved by the University of North Dakota Institutional Review Board and registered with ClinicalTrials.gov, numbers NCT02444247 and NCT02416882.

For both studies, after having the study explained and providing written informed consent, participants provided a blood sample for genetic assessment and were given an ActiGraph accelerometer (Pensacola, FL) to measure usual PA. Participants wore the accelerometer for seven days before performing additional assessments. During subsequent visits, participants completed assessments of anthropometrics (height and weight), exercise reinforcement, and tolerance for discomfort during intense exercise.

Table 1
Demographics, MVPA, and exercise reinforcement of the study participants.

	Male (n = 51)	Female (n = 127)	Total (n = 178)
Age (years)	26.3 ± 6.7	27.1 ± 9.3	26.9 ± 8.6
BMI (kg/m^2)[1]	27.0 ± 5.1*	25.2 ± 4.4*	25.7 ± 4.7
$RRV_{exercise}$[2]	0.72 ± 0.34	0.71 ± 0.37	0.71 ± 0.4
MVPA[3]	50.4 ± 27.3*	35.7 ± 22.9*	40.0 ± 25.1
Preference[4]	26.1 ± 5.5	26.3 ± 6.2	26.3 ± 6.0
Tolerance[5]	26.0 ± 5.7*	23.9 ± 5.2*	24.5 ± 5.4

Data are presented as mean ± SD.
*means differ ($p \leq 0.05$) between sex.
[1] BMI: body mass index.
[2] RRV_{AT}: number of sessions completed during the RRV task to gain access to aerobic exercise. training (AT) when sedentary behavior was available as a behavioral alternative.
[3] MVPA: minutes of moderate to vigorous physical activity per week.
[4] Preference: Preference for the Intensity of Exercise Questionnaire score (au).
[5] Tolerance: Tolerance of the Intensity of Exercise Questionnaire score (au).

2.2. Assessments

2.2.1. Height and weight

Height was measured in triplicate to the nearest 0.1 cm using a stadiometer (Seca; Chino, CA). Body weight was measured using a calibrated digital scale (Fairbanks Scales- Model SCB-R9000-HS; MO) to the nearest 0.1 kg. Measures were completed with participants wearing either provided lab scrubs or light casual clothes (t-shirt, shorts) and not wearing shoes.

2.2.2. Physical activity

Habitual, free-living PA was measured using an ActiGraph accelerometer (GT3X + model; Pensacola, Florida). Each participant wore the device for seven days prior to performing other assessments. Participants were instructed to wear the monitor at the right hip using the provided belt during all hours awake except when bathing or swimming. Data were cleaned of non-wear time, defined as consecutive strings of zeros greater than 20 min. An epoch of 10 s was used for data collection as a shorter epoch is more suitable to reflect bout duration under free-living conditions where many bouts of sporadic PA last 30 s or less [33,34]. These data were used to determine participants' usual PA, defined as weekly minutes of MVPA using the Crouter et al. algorithm [35] and Freedson cut-points [36].

2.2.3. Liking

Participants' liking (hedonic value) of the exercise options (treadmill, elliptical, stationary bike) and sedentary alternatives (TV, video games, reading magazines, puzzles/Sudoku) was assessed using a 10-point scale (1 = "do not like at all" and 10 = "like very much"). The most liked sedentary activity and exercise option was used as the sedentary and exercise alternative for the $RRV_{exercise}$ testing session, respectively.

2.2.4. $RRV_{exercise}$

Participants' $RRV_{exercise}$ (specifically, aerobic-type exercise) was assessed against a sedentary alternative chosen based upon hedonic liking scores (see "Liking" above). $RRV_{exercise}$ was assessed by evaluating the amount of operant responding (mouse button presses) a participant was willing to complete to gain access to exercise or a sedentary alternative [11,37]. The testing space included two adjacent

computer workstations. The participant could earn points towards their most liked exercise activity at one station, while the other station was an identical setup that could be used to earn points toward their most liked sedentary alternative. Participants could switch between stations as much as they chose. The program presented a game similar to a slot machine with a row of three shapes of various colors; a point was earned each time the shapes and colors matched. For every 5 points a schedule was completed and the participant received 5 min of access to the reinforcer that was earned (either exercise or sedentary activity). The game was performed until the participant no longer wished to work for access to either the exercise or sedentary activities, with no minimum or maximum time limit. At first, points were delivered after every 4 presses (schedule of reinforcement was 4), but then the schedule of reinforcement doubled (4, 8, 16, 32, […] 1024) each time 5 points were earned. For instance, the participant initially had to click the mouse button 4 times to earn one point for schedule 1. After the first 5 points were earned, schedule 1 was complete and the participant had earned 5 min for the corresponding activity. Then, 8 clicks were required to earn each of the next 5 points for schedule 2 before another 5 min was earned. Schedule 3 required 16 clicks to earn one point, schedule 4 required 32 clicks to earn one point, and so on [11,37]. Participants engaged in the activity for the time earned after they complete the reinforcement task, which ended when participants no longer wished to earn points (time) for exercise or the sedentary alternative. Similar button pressing tasks have been used as valid predictors of the RRV of physical versus sedentary activity [7]. Participants self-selected the intensity level when performing any earned exercise time, which was typically a low to moderate steady-state intensity. These assessments took place in private laboratory space within a large exercise facility. Participants completed their earned exercise time using the exercise facilities' equipment. The last schedule completed for exercise and the sedentary alternative were assessed separately and termed Pmax of sedentary ($Pmax_{sed}$) and Pmax of exercise ($Pmax_{exercise}$). $RRV_{exercise}$ was calculated as ($Pmax_{exercise}$/($Pmax_{exercise}$ + $Pmax_{sed}$)) [18,37].

2.2.5. Preference and tolerance for exercise intensity

Participants completed the Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q) [38]. The tolerance subscale measured ability to tolerate the discomfort associated with intense exercise and was included in the current analysis as only tolerance scores have been linked to $RRV_{exercise}$ [6].

2.2.6. Genetic assessment

Table 2 details the SNPs assessed. SNP genotyping was performed on 3–5 ml samples of whole blood collected in EDTA-containing tubes that were immediately processed for DNA extraction and frozen for future batch analysis. Platinum® qPCR SuperMix for SNP Genotyping (Applied Biosystems' TaqMan®-based SNP genotyping products, Life Technologies) specifically formulated for discrimination of alleles by real-time qPCR followed by allelic-discrimination analysis was used for the amplification and identification of each SNP. Predesigned SNP genotyping assays for individual SNPs that included two allele-specific TaqMan® MGB probes containing distinct fluorescent dyes and a PCR primer pair to detect specific SNP targets were used. These probe and primer assays align with the genome to provide specificity for the allele of interest.

2.3. Analytic plan

Sex differences in demographics, $RRV_{exercise}$, MVPA, liking, and tolerance for exercise discomfort were determined by unpaired T-tests. One-way analysis of variance (ANOVA) tested whether participants homozygous for minor alleles differed for $RRV_{exercise}$, tolerance of exercise intensity, MVPA, and liking of exercise and sedentary activities from participants carrying one or two major alleles. $RRV_{exercise}$ was modeled using the beta distribution due to it being a ratio score. When used as a dependent variable, MVPA was transformed by natural logarithmic transformation due to the highly skewed distribution, and back-transformed to report means and standard errors in models predicting MVPA. All other dependent variables were modeled using the normal distribution. For SNPs that showed significant differences by ANOVA, after correcting for the false discovery rate, multiple regressions were performed to test whether SNP genotype was predictive of $RRV_{exercise}$, tolerance for exercise intensity, or MVPA after controlling for possible covariates. The $RRV_{exercise}$ model included BMI, MVPA, tolerance for exercise intensity, liking of aerobic exercise, and sex as covariates. Tolerance of exercise intensity models included BMI, MVPA, $RRV_{exercise}$, liking of exercise, and sex. The MVPA model included BMI, $RRV_{exercise}$, liking of aerobic exercise, tolerance for exercise intensity, sex, and the interaction of tolerance and genotype.

3. Results

Men had greater ($p < 0.05$) BMI, MVPA, and tolerance for exercise intensity than women. No sex differences were found for age or $RRV_{exercise}$, (Table 1). Genotype prevalence was consistent with NIH databases (https://www.ncbi.nlm.nih.gov/snp/) as shown in Table 3.

Participants that were homozygous (A:A) for rs1800497 had a lower $RRV_{exercise}$ than participates carrying one or two G alleles when tested by ANOVA ($p < 0.01$) and by regression ($p < 0.01$) that modeled potential covariate effects on $RRV_{exercise}$ (Table 4). From ANOVA, tolerance for exercise intensity was greater ($p < 0.05$) for participants that were homozygous for rs6454672 (T:T), and lower for homozygous rs8036270 (A:A) and rs12405556 (G:G) ($p < 0.01$, $p < 0.05$, respectfully). Results from the regression models demonstrated that SNP's rs6454672, rs8036270, and rs12405556 were significant ($p < 0.03$) predictors of tolerance for exercise intensity. MVPA and $RRV_{exercise}$ were also significant ($p < 0.01$) predictors of tolerance for exercise intensity in each model (Table 5). SNP rs6454672 was a significant predictor ($p < 0.001$) of MVPA, as homozygous carriers of the T allele exhibited lower ($p < 0.01$) MVPA (Table 6). The interaction of tolerance and genotype was tested to further examine the synergy between genotype and the ability to tolerate exercise intensity but was not significant ($p = 0.41$). There were no SNP genotypes that influenced in liking of the exercise or sedentary alternatives.

4. Discussion

This is the first investigation of the association of SNPs that moderate central dopamine physiology and pain neurotransmission with exercise reinforcement, tolerance for exercise intensity, and usual physical activity. The results support the hypothesis that a genetic contribution to $RRV_{exercise}$ exists. Specifically, individuals carrying the polymorphism of a G allele at rs1800497 had greater $RRV_{exercise}$. The rs1800497 polymorphism, also known as Taq1A, affects the ankyrin repeat and kinase domain containing 1 gene (ANKK1), and is a G > A polymorphism, causing a Glutamine > lysine missense variant. Although there is some debate [39], Taq1A is associated with decreased ligand binding at, or decreased expression of the dopamine D2 receptor (DRD2) [40–43], and is associated with other reinforcing behaviors [30] and greater risk of alcohol and drug abuse [44]. Further, central dopamine signaling is necessary for development and maintenance of exercise behavior [24], supporting a role for Taq1A in exercise reinforcement. Indeed, genotype variants affecting dopamine signaling via DRD2 or ANKK1 expression are associated with differences in usual physical activity in both rodents and humans [45,46].

In the current study, homozygous Taq1A carriers (A1/A1) had lower ($p < 0.01$) $RRV_{exercise}$ than heterozygous A1:A2 or homozygous A2/A2 carriers (Table 4). Adults with the Taq1A allele experience a decreased response to reinforcing stimuli [30]. Notably, dopamine signaling has been investigated for its role in motivation [47,48], motor movement

Table 2
List of single nucleotide polymorphisms (SNPs) assessed in the present study.

SNP ID	Gene	Polymorphism	Residue Change
rs8066276	ACE	C/T Transition Substitution (TCT**[C/T]**ACT)	N/A
rs11615016	TPH2	A/G transition substitution (TAC**[A/G]**TTC)	N/A Intron Variant
rs6454672	CNR1	C/T Transition Substitution (CTT**[C/T]**ACA)	N/A Intron Variant
rs6280	DRD3	C/T Transition Substitution (GGC**[C/T]**ACT)	C [Gly] ⇒ S [Ser]
rs8049933	FTO	C/T Transition Substitution (AAT**[C/T]**GGT)	N/A Intron Variant
rs9936768	FTO	C/T Transition Substitution (TAT**[C/T]**GTC)	N/A Intron Variant
rs12446047	FTO	C/T Transition Substitution (GAC**[C/T]**TCA)	N/A Intron Variant
rs11076022	FTO	A/G transition substitution (GTC**[A/G]**TTC)	N/A
rs7199716	FTO	C/T Transition Substitution (TTC**[C/T]**CTC)	N/A Intron Variant
rs6314	HTR2A	A/G transition substitution (AAT**[A/G]**CTG)	A [His] ⇒ G [Tyr]
rs1800497	DRD2/ANKK1	A/G transition substitution (GTC**[A/G]**AGG)	A [Glu] ⇒ G [Lys]
rs10887741	PAPSS2	C/T Transition Substitution (GGG**[C/T]**TCC)	N/A Intron Variant
rs12612420	None	A/G transition substitution (TCC**[A/G]**GAT)	N/A
rs8097348	None	A/G transition substitution (TA**[A/G]**CTAG)	N/A
rs12405556	LEPR	G/T Transversion Substitution (CAG**[G/T]**ATA)	N/A Intron Variant
rs8036270	GABRG3	A/G transition substitution (GAA**[A/G]**TGA)	N/A Intron Variant
rs6265	BDNF	C/T Transition Substitution (TCA**[C/T]**GTG)	C [Val] ⇒ T [Met]
rs1076560	DRD2	A/C Transversion Substitution (TC**[A/C]**CCC)	N/A Intron Variant
rs4680	COMT	A/G transition substitution (GGC**[A/G]**TGA)	G [Val] ⇒ A [Met]
rs265981	DRD1	A/G transition substitution (GGC**[A/G]**GCC)	N/A
rs1800955	DRD4	C/T Transition Substitution (GGG**[C/T]**GCG)	N/A
rs1611115	DBH	C/T Transition Substitution (TTG**[C/T]**GGG)	N/A
rs6275	DRD2	A/G transition substitution (ACC**[A/G]**TGG)	A [His] ⇒ G [His]

Table 3
prevalence of genotypes with significant predictive values.

SNP	Allele	Frequency	Percent	Genotype	Frequency	Percent
rs1800497	A:A	10	5.6	All A	10	5.6
	A:G	52	29.2	Has G	168	94.4
	G:G	116	65.2			
rs6454672	C:C	28	15.8	Has C	116	65.5
	C:T	88	49.7			
	T:T	61	34.5	All T	61	34.5
rs8036270	A:A	52	29.2	All A	52	29.2
	A:G	88	49.4	Has G	126	70.8
	G:G	38	21.4			
rs12405556	G:G	84	47.2	All G	84	47.2
	G:T	80	44.9	All T	94	52.8
	T:T	14	7.9			

Table 4
ANOVA results and regression model results predicting the relative reinforcing value of exercise from SNP rs1800497 and covariates.

	Coefficient ± SE	P
Full regression model		
R^2 = 0.11		
Intercept	−1.10 ± 1.01	0.28
BMI	−0.01 ± 0.02	0.55
MVPA	0.003 ± 0.004	0.43
Tolerance	0.03 ± 0.02	0.14
Liking of exercise	0.16 ± 0.08	0.05
Sex = Female	−0.02 ± 0.23	0.94
rs1800497 A:A	−1.20 ± 0.42	0.005
Regression model of significant predictors		
R^2 = 0.06		
Intercept	0.75 ± 0.11	< 0.001
rs1800497 A:A	−1.38 ± 0.42	0.001
RRV by genotype (from ANOVA)		
Genotype	Mean ± SE	
AA	0.35 ± 0.09*	
AG,GG	0.68 ± 0.02*	

Single nucleotide polymorphism (SNP), body mass index (BMI), moderate-to-vigorous physical activity (MVPA), tolerance for exercise intensity (Tolerance), sex coded as: female = 0, male = 1.

* Means ± SE differ ($p < 0.01$).

[49–51] and reinforcement [52]. Moreover, the dopamine system is a key player in determining voluntary physical activity (see review (24)). Antagonists of DRD_2 receptors [53] or similar DRD_2 polymorphisms [46] also reduce motor activity in humans. Together these data support a mechanism by which Taq1A inhibits central dopamine signaling, therefore attenuating $RRV_{exercise}$.

This study is also the first to demonstrate a genotypic association with tolerance for exercise intensity. The SNP's rs6454672, rs8036270, and rs12405556 independently predicted tolerance for exercise intensity, which is defined as an individual's ability to tolerate the discomfort associated with intense exercise such as fatigue, pain, and sweatiness [38]. This is in contrast to the need to increase dosage to maintain a response, as is common with pharmacologic agents. Greater tolerance for exercise intensity is associated with participating in enough exercise to meet physical activity guidelines [6] and with self-selected exercise intensity [54], suggesting that greater tolerance for exercise intensity may lead to more frequent engagement in intense physical activity.

Most of what is known regarding rs6454672 is in respect to cannabinoid signaling and schizophrenia, as rs6454672 is located near the cannabinoid receptor 1 gene and is noted for its contribution to genetic coding variability for the cannabinoid receptor type 1 (CB1) gene [55]. Stimulation of CB1 receptors negatively regulates pain and inflammation through its inhibitory action as a Gαi-coupled receptor, decreasing neurotransmission of pain [56]. Carrying even a single minor (C) allele is associated with a decreased likelihood of meeting physical activity recommendations [57], which is supported by the current finding that homozygous T carriers have greater tolerance for exercise intensity, supporting previous work demonstrating individuals with greater tolerance for exercise intensity are more likely to meet PA recommendations [6]. The relationship between tolerance for exercise intensity and increased likelihood of meeting PA recommendations is also supported by the current finding that participants homozygous (T:T) at rs6454672 also exhibited greater MVPA. However, no other SNP's tested in this study were associated with MVPA.

The gamma-aminobutyric acid type A receptor gamma 3 subunit (GABRG3) encodes a gamma-aminobutyric acid (GABA) receptor and rs8036270 is an intron variant within this gene locus. GABA, as the primary inhibitory neurotransmitter in the human brain, can bind to ionotropic receptors (K + channels - hyperpolarizing) or metabotropic receptors (Gαi) to inhibit neurotransmission of painful stimuli [58].

Table 5
ANOVA results and regression model results predicting tolerance for exercise intensity from SNP rs6454672, rs8036270 or rs12405556, and covariates.

rs6454672			rs8036270			rs12405556		
Coefficient ± SE		P	Coefficient ± SE		P	Coefficient ± SE		P
Full regression models								
R^2 = 0.21			R^2 = 0.24			R^2 = 0.21		
Intercept	19.36 ± 4.31	< 0.001	Intercept	20.27 ± 4.19	< 0.001	Intercept	20.33 ± 4.31	< 0.001
BMI	0.06 ± 0.10	0.58	BMI	0.06 ± 0.10	0.57	BMI	0.04 ± 0.10	0.73
MVPA	0.05 ± 0.01	< 0.001	MVPA	0.06 ± 0.02	< 0.001	MVPA	0.06 ± 0.01	< 0.001
$RRV_{Exercise}$	2.95 ± 1.09	0.008	$RRV_{Exercise}$	3.17 ± 1.12	0.005	$RRV_{Exercise}$	2.88 ± 1.14	0.01
Liking of exercise	−0.03 ± 0.38	0.95	Liking of exercise	−0.03 ± 0.37	0.93	Liking of exercise	0.12 ± 0.37	0.75
Sex = Female	−1.40 ± 0.96	0.15	Sex = Female	−1.10 ± 0.99	0.27	Sex = Female	−1.52 ± 1.02	0.14
rs6454672 T:T	2.12 ± 0.90	0.02	rs8036270 A:A	−2.86 ± 0.89	0.002	rs12405556 G:G	−1.86 ± 0.82	0.025
Regression models of significant predictors								
R^2 = 0.19			R^2 = 0.21			R^2 = 0.19		
Intercept	19.40 ± 0.91	< 0.001	Intercept	20.67 ± 1.0	< 0.001	Intercept	20.88 ± 1.02	< 0.001
rs6454672 T:T	2.39 ± 0.88	0.007	rs8036270 A:A	−2.95 ± 0.82	< 0.001	rs12405556 G:G	−2.08 ± 0.77	0.0072
MVPA	0.06 ± 0.01	< 0.001	MVPA	0.07 ± 0.01	< 0.001	MVPA	0.063 ± 0.01	< 0.001
$RRV_{Exercise}$	2.72 ± 1.03	0.009	$RRV_{Exercise}$	2.86 ± 1.05	0.007	$RRV_{Exercise}$	2.90 ± 1.11	0.0096
Tolerance by genotype (from ANOVA)								
Genotype	Mean ± SE			Mean ± SE			Mean ± SE	
TT	26.04 ± 0.73*		AA	22.41 ± 0.69**		GG	23.41 ± 0.58*	
CT,CC	23.65 ± 0.46*		AG,GG	25.36 ± 0.45**		GT,TT	25.49 ± 0.51*	

*means ± SE differ between genotype ($p < 0.05$).
**means ± SE differ between genotype ($p < 0.01$).
Single nucleotide polymorphism (SNP), body mass index (BMI), moderate-to-vigorous physical activity (MVPA), tolerance for exercise intensity (Tolerance), sex coded as: female = 0, male = 1.

Table 6
ANOVA results and regression model results predicting the natural logarithm of daily minutes of moderate-to-vigorous physical activity from SNP rs6454672 and covariates.

Coefficient ± SE		P
Full regression model		
R^2 = 0.22		
Intercept	3.38 ± 0.55	< 0.001
BMI	−0.01 ± 0.01	0.32
$RRV_{Exercise}$	0.09 ± 0.15	0.54
Liking_AT	−0.02 ± 0.04	0.71
Tolerance	0.02 ± 0.01	0.02
rs6454672 T:T	0.35 ± 0.10	< 0.001
Sex = Female	−0.37 ± 0.09	< 0.001
Regression model of significant predictors		
R^2 = 0.19		
Intercept	3.01 ± 0.23	< 0.001
Tolerance	0.02 ± 0.01	0.01
Sex = Female	−0.30 ± 0.10	0.002
rs6454672 T:T	0.32 ± 0.09	< 0.001
MVPA by genotype (from ANOVA)		
Genotype	Mean ± SE	
TT	42.95 ± 2.48*	
CT,CC	31.1 ± 2.1*	

Single nucleotide polymorphism (SNP), body mass index (BMI), relative reinforcing value of exercise ($RRV_{Exercise}$) tolerance for exercise intensity (Tolerance), ANOVA model means and standard errors are back-transformed from natural logarithmic function.
*means ± SE differ ($p < 0.01$).

Consistent with the present finding that carrying at least one G allele at rs8036270 predicts increased tolerance for exercise intensity, prior studies have determined that this SNP is also associated with leisure time exercise behavior and physical activity related energy expenditure [26,59]. Although further research is necessary for verification, these findings suggest that rs8036270 positively regulates inhibitory neurotransmission through GABA signaling, thus decreasing "pain" signaling pathways, increasing exercise intensity tolerance, and therefore, physical activity.

SNP rs12405556 is an intron variant that affects the leptin receptor and predicts physical activity [59,60]. In agreement with the current study, prior studies have also demonstrated that glutamine to arginine substitution in codon 223 of the leptin receptor predicts levels of physical activity and adiposity in humans [60]. The current work revealed that having at least one copy of the minor (T) allele predicted greater tolerance for exercise intensity. Central leptin receptors, and therefore central leptin signaling, play key roles in feeding behavior [80], energy homeostasis [61], and physical activity behavior [60,62]. Therefore, these data suggest that carrying at least one copy of the minor allele for rs12405556 may be a genetic factor driving greater tolerance for exercise intensity, and physical activity.

5. Conclusion

In conclusion, we found that SNP rs1800497 predicted $RRV_{exercise}$. Additional SNP's rs6454672, rs8036270 and rs12405556 predicted greater tolerance for exercise intensity, while rs6454672 also predicted MVPA. Having greater $RRV_{exercise}$ is an important factor in one's choice to be more physically active [6,8,63]. Maintaining an exercise routine likely depends on an individual's ability to experience aversive aspects of exercise yet be able to tolerate those unpleasant aspects and persist engaging in exercise behavior. Therefore, having greater $RRV_{exercise}$ and tolerance for the discomfort associated with intense exercise may lead to more frequent and sustained exercise behavior. These results demonstrate that functional changes at the protein level provide pathways by which SNPs may be driving changes in physical activity-related behavior, and these SNPs may be underlying causes for differences in habitual physical activity between individuals. Further research to determine personalized exercise prescriptions based on genotype, along with strategies to increase exercise reinforcement among certain individuals is needed to potentially increase the number of Americans being physically active.

Contributions

Kyle D. Flack, PhD., RD: Lead author. Contributed to study design and development, led all aspects of recruitment, intervention management, and data collection. Composed an original manuscript draft.

Christopher Pankey: Second author. Revised all manuscript drafts and completed writing of the manuscript.

Kelsey Elise Ufholz, PhD.: Third author. Assisted in data collection and composition of manuscript.

LuAnn Johnson, MS: Fourth author. Statistician in charge of all statistical analysis.

James N. Roemmich, PhD.: Senior author. Led study idea development, study design, and responsible for funding. Revised all manuscript drafts and made final decisions on manuscript and data analysis.

All authors have approved the final version of the manuscript.

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Data statement

Raw data available upon request to the Grand Forks Human Nutrition Research Center Data Sharing Committee: phone: 701-795-8272, fax: 701-795-8230

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